Review

The Case for a Genetic Predisposition to Serrated Neoplasia in the Colorectum: Hypothesis and Review of the Literature

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Abstract

In recent years, an alternative pathway of colorectal cancer development has been described in which serrated polyps replace the traditional adenoma as the precursor lesion. Importantly, serrated polyps and a subset of colorectal cancer show largely nonoverlapping mutation profiles to those found in adenomas and the majority of colorectal cancer. These genetic alterations include activating mutation of the *BRAF* proto-oncogene and widespread gene promoter hypermethylation (CpG island methylator phenotype or CIMP). Up to 15% of colorectal cancer is likely to develop on the basis of a strong genetic predisposition. The two most well-characterized syndromes, familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer (Lynch syndrome), both develop via the adenoma-carcinoma pathway and together account for approximately one third of familial colorectal cancer. We have recently described 11 families in which there is evidence that the genetic predisposition to autosomal dominant colorectal cancer is linked to the serrated pathway. This condition, serrated pathway syndrome, and the related condition, hyperplastic polyposis, the presentation of which suggests a recessive mode of inheritance, represent two syndromes in which *BRAF* mutation and methylation co-occur within serrated precursor lesions. Further, CIMP is observed in the normal colonic mucosa of individuals with hyperplastic polyposis consistent with a field defect in epigenetic regulation. The spectrum of serrated neoplasia may also implicate the apparently sporadic and later onset subset of colorectal cancer with high levels of microsatellite instability. The tendency for these lesions to be multiple, associated with smoking, and to show frequent *BRAF* mutation and CIMP points to a defect that may result from interactions between the environment and a weakly penetrant genetic alteration. (Cancer Epidemiol Biomarkers Prev 2006;15(10):1778–84)

Introduction

Colorectal cancer has provided a paradigm for the study of molecular pathology in solid tumors. In 1988, Vogelstein et al. (1) developed a molecular model that was based on careful analysis of the mutations occurring within particular developmental stages of colorectal cancer. The progressive accumulation of a critical number of mutations over a period of years, with each genetic change being associated with an evolutionary step in neoplastic transformation, represented the molecular counterpart of the adenoma-carcinoma sequence (2). These steps included initiating mutations of the tumor-suppressor gene *APC*, activating point mutations in *KRAS* driving progression, and mutations in *TP53* associated with malignant transformation. The model emphasized the central importance of the adenomatous polyp as the precursor lesion for most colorectal cancer, and centered upon a mechanism of tumorigenesis known as chromosomal instability. Publication of the model encouraged an extraordinary expansion of research based on molecular dissection of the developmental pathway to malignancy. Since its introduction, however, new evidence has led to the identification of an alternative and possibly rapidly evolving pathway separate from that proposed by Vogelstein et al. (3, 4). This alternative pathway, in which serrated polyps replace the traditional adenoma as the precursor lesion to colorectal cancer, has become known as the serrated pathway. Importantly, the serrated pathway displays mutation profiles that are largely nonoverlapping with those of the traditional adenoma-carcinoma pathway, including a tight association between widespread DNA methylation (CpG island methylator phenotype or CIMP), and activating mutations in the *BRAF* proto-oncogene (5-7). In this article, we review the evidence that a subset of familial colorectal cancer evolves via this pathway, based on the frequent occurrence of advanced serrated lesions; *BRAF* mutation; and CIMP in (*a*) multicase colorectal cancer families with an autosomal dominant inheritance, (*b*) rare sibships and individuals with multiple serrated lesions and a recessive mode of inheritance, and (*c*) high-level microsatellite instability (MSI-H) sporadic colorectal cancer in which synchronous and metachronous lesions are over five times more likely to occur than in the balance of colorectal cancer.

The Serrated Pathway of Colorectal Cancer Development

The concept that almost all colorectal cancers develop within benign adenomatous precursor lesions has been promulgated for decades. Epithelial polypoid lesions in the colorectum are relatively common in Western populations and occur with increasing age. Besides the traditional adenoma, upon which the Vogelstein model is based, another common lesion is the hyperplastic (metaplastic or serrated) polyp, which has been widely dismissed as innocuous. However, a new understanding of the pathology and natural history of hyperplastic polyps has emerged over the past decade (3, 4, 8-23). Serrated polyps encompass the common hyperplastic polyps found most

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frequently in the distal bowel of older patients, and also occurring as satellite nodules around rectal cancers that regress after resection (24). These can be easily distinguished from adenomas by their histologic appearance and are highly unlikely to progress to malignancy. The simple hyperplastic polyp has itself been subclassified into a goblet cell variant and a microvesicular variant (23). However, serrated polyps also include a broader spectrum of polyp subtypes ranging from these small common lesions to the recently described sessile serrated adenoma (SSA), which is often large and proximal with abundant mucin secretion, exaggerated serration, and atypical architecture (12, 23). Importantly, SSA have definite malignant potential (5, 10). Rarer serrated polyp subtypes with unequivocal dysplasia include traditional serrated adenoma (SA), which combines the dysplastic features of an adenoma with the architectural features of a hyperplastic polyp (16, 19, 25) and the mixed polyp (MP) in which separate hyperplastic and dysplastic elements are combined within a single polyp (Table 1; Fig. 1). SSA, SA, and MP are described as ''advanced serrated polyps'' and comprise ~5% of all serrated polyps retrieved in colonscopy patients (26). Importantly, these advanced serrated lesions show frequent *BRAF* mutation and widespread DNA methylation (5).

A Genetic Predisposition to Serrated Neoplasia

It has been estimated that up to 15% of colorectal cancer occurs as part of a strong genetic predisposition. In a significant proportion of these families, the number and distribution of affected individuals implicates a single dominantly inherited mutation (27). A further unknown proportion may be due to subtle genetic influences, which alter the metabolism of extrinsic or endogenous carcinogens (28). In the past decade, much progress has been made in achieving the genetic characterization of two major forms of hereditary colorectal cancer predisposition, namely familial adenomatous polyposis and hereditary nonpolyposis colon cancer (Lynch syndrome). Both are inherited as autosomal dominant conditions in which affected subjects develop early-onset colorectal cancer. However, familial adenomatous polyposis and Lynch syndrome together account for only 2% to 5% of all colorectal cancer, indicating that there are still many families in which the nature of the underlying genetic cause of the family cancers remains to be identified. Familial colorectal cancer also includes recessive modes of inheritance of proximal cancers determined in a population-based family data set (29), mutations in the *MYH* DNA repair gene (30-32) and a series of non–Lynch syndrome familial colorectal cancer with an autosomal dominant mode of inheritance described by Lindor and colleagues and confirmed by subsequent studies (33-35). Both familial adenomatous polyposis and Lynch syndrome are associated with the traditional adenoma-carcinoma pathway. The possibility of a familial syndrome with origins in the serrated pathway has been considered only recently, although was first proposed by Jeevaratnam et al. (36) in 1996, and further explored by Jass et al. (37) in 1997.

Hyperplastic Polyposis as a Predisposition to Serrated Neoplasia

Individuals with numerous large serrated polyps occurring throughout the colon have been recognized for decades outside the familial setting (38). Known as hyperplastic polyposis (HPP), the disorder was originally highlighted to distinguish it from familial adenomatous polyposis (39, 40). Initially, HPP was assumed to have no malignant potential. Subsequently, cases of HPP with synchronous adenocarcinoma have been increasingly reported (13, 18, 41-47). In the late

Table 1. Features of colonic polyp subtypes

Polyp name	Alternative terminology	Morphology and significance	Molecular features
Adenoma	Adenomatous polyp	Neoplastic polyp with malignant potential	*BRAF* mutation and CIMP rare (5, 92)
Serrated polyp	Various (see below)	General term for all colorectal polyps with glandular serration	
Hyperplastic polyp, goblet type	Type 1 hyperplastic polyp	Subtype of hyperplastic polyp with conspicuous goblet cells and showing the least morphologic deviation from normal; described as goblet-cell rich type. Found predominantly in the distal colon	Frequent *KRAS* mutation (54%; ref. 89)
Hyperplastic polyp, microvesicular type	Type 2 hyperplastic polyp	Variant of hyperplastic polyp in which columnar cells have mucin-filled vesicles within the apical cytoplasm and goblet cells are relatively inconspicuous	Frequent *BRAF* mutation (76%) and CIMP (68%; ref. 89)
SSA	Sessile serrated polyp. Serrated polyp with atypical proliferation	Advanced type of serrated polyp with abnormalities of architecture and proliferation but lacking the classic features of epithelial dysplasia (intraepithelial neoplasia)	Frequent *BRAF* mutation (75-82%) and CIMP (92%; refs. 5, 89)
MP	Admixed polyp	Rare serrated polyp that includes two separate components. One component is usually nondysplastic (usually SSA) whereas the second dysplastic component is either traditional adenoma or serrated adenoma; partly hyperplastic polyp and partly adenoma. Polyps with mixtures of adenoma and SA have also been described as mixed polyps	Frequent *BRAF* mutation, especially when SSA forms part of the lesion (89%; ref. 5)
SA	(*a*) Mixed hyperplastic adenomatous polyp. (*b*) Atypical hyperplastic polyp. (*c*) Traditional SA	Relatively rare neoplastic polyp having a serrated architecture reminiscent of hyperplastic polyp but with unequivocal traditional adenomatous dysplasia. Comprises <5% of serrated polyps	Marked molecular heterogeneity. Overlapping molecular pathways. May have either *KRAS* or *BRAF* mutation or and features of the adenoma-carcinoma pathway

NOTE: Data are adapted from ref. 16.

1990s, HPP was acknowledged as a condition carrying an increased risk for malignant transformation. Individuals with HPP present with synchronous cancers of the colorectum in approximately one half of the cases (44, 48). Because HPP is a relatively rare condition and examples associated with colorectal cancer are likely to present for symptomatic reasons, it is difficult to determine the overall proportion of cases that will develop colorectal cancer. However, cases with large, atypical, and dysplastic polyps appear to be at the highest risk for presenting with a synchronous colorectal cancer (44). HPP is a relatively late-onset disorder, usually diagnosed in the fifth to the seventh decades of life, although it can occur earlier (49, 50). Polyp numbers range from 5 to well over 100, with most cases having between 40 and 100 lesions (51). A characteristic feature of HPP is the diverse range of polyp types, ranging from diminutive hyperplastic polyps to larger SSA, SA, and MP as well as traditional adenomas (52-54). Recently, Burt and Jass (55) developed a working definition of HPP, namely (*a*) at least five proximal hyperplastic polyps two of which are >10 mm in diameter, or (*b*) any number of HPs proximal to the sigmoid colon in an individual with a first-degree relative with HPP, or (*c*) >20 hyperplastic polyps distributed throughout the colon.

It was initially thought that HPP was not associated with a family history of HPP or colorectal cancer in first-degree relatives. However, HPP may sometimes occur in several members of the same family (36, 37, 45), whereas colorectal cancer occurs in 27% of relatives of cases with HPP (45). Fourteen patients studied in a Portuguese series reported 57% of first-degree relatives with polyps and 33% with a family history of colorectal cancer (51). In contrast, a study of 15 cases of HPP from Utah found no evidence of HPP or any spectrum cancers in relatives, although it was not clear whether this study had excluded cases with satellite lesions in the distal colon (56). The rare existence of sibships, and consanguineous families with HPP (57) suggests a recessively inherited basis for the initiation of this condition.

Widespread DNA methylation (CIMP) and *BRAF* mutation have been reported in the serrated neoplasms of patients with HPP (58, 59), reflecting the signature changes of the serrated pathway observed in their sporadic counterparts (5, 7). The presence of a *BRAF* mutation in a serrated lesion from a patient with multiple hyperplastic polyps was at least five times more likely to be associated with a second *BRAF* mutation–bearing lesion than if the index lesion did not harbor such a mutation (59). The concept of a field defect in colonic mucosa is well shown in a penetrant genetic predisposition such as familial adenomatous polyposis. Similarly, in HPP, hypermethylation of multiple gene promoters is not confined to the neoplastic tissues. Minoo and colleagues (60-62) have recently shown a significant difference in the number of methylated markers seen in apparently normal mucosa of HPP when compared with cases with sporadic serrated lesions (85-90% versus 13%), further supporting the hypothesis that HPP is associated with an underlying and genetically determined field change. Two examples of families in which HPP is present are shown in Fig. 2A.

Serrated Pathway Syndrome

Evidence also exists for an autosomal dominant predisposition to serrated neoplasia. We have recently described 11 MSI-variable (MSI-V) colorectal cancer families in which there are

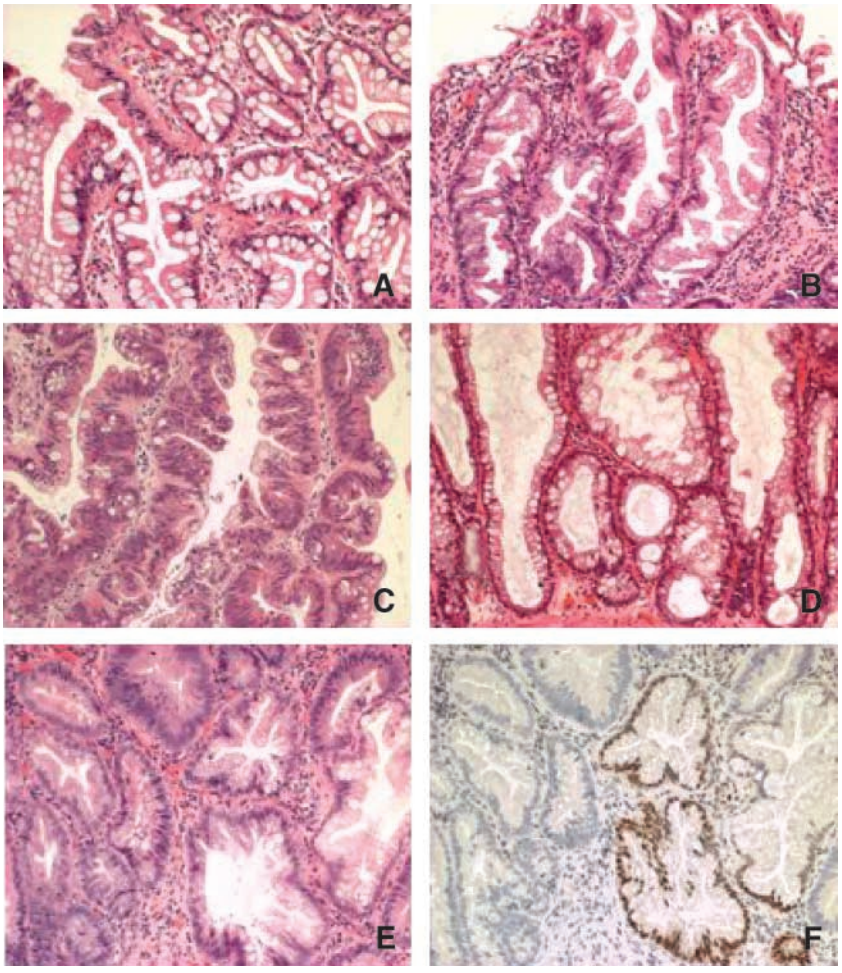

Figure 1. Examples of serrated polyp subtypes. **A.** Goblet cell type hyperplastic polyp, a polyp subtype with normal proliferation, conspicuous goblet cells, and minimal morphologic deviation from normal mucosa. **B.** Microvesicular type hyperplastic polyp, also with essentially normal proliferation but with prominent columnar cells with mucin-filled microvesicles in apical cytoplasm and increased serration. **C.** Traditional SA, a lesion with serrated architecture but with unequivocally dysplastic or adenomatous epithelium. **D.** SSA, a subtype with exaggerated serration, architectural changes, increased proliferation, but with cytologic changes falling short of dysplasia. **E.** Mixed polyp, composed of nondysplastic SSA and a dysplastic component with morphology resembling conventional adenoma or traditional SA. **F.** Loss of MLH1 expression in the dysplastic portion of the mixed polyp. SA, SSA, and MP are described as advanced serrated polyps to indicate their increased malignant potential compared with goblet cell type hyperplastic polyp and microvesicular type hyperplastic polyp.

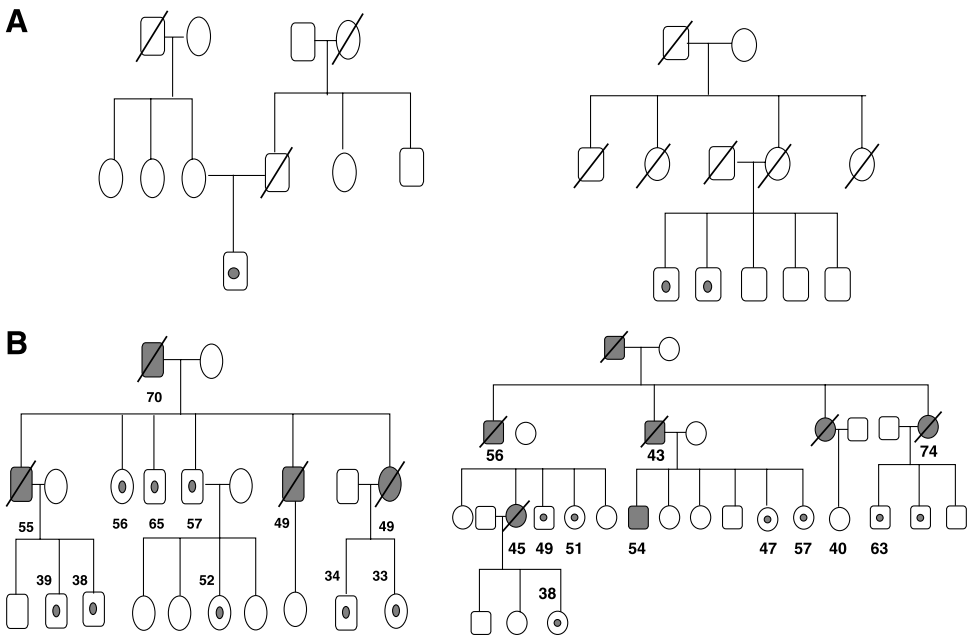

Figure 2. **A**, two HPP pedigrees showing possible recessive inheritance and a single individual and a sibship respectively with multiple serrated polyps (*dotted symbols*). **B**, two multicase colorectal cancer families showing affected individuals with colorectal cancer (*filled symbols*) and advanced or multiple serrated polyps (*dotted symbols*), and their ages of onset.

interesting clinical, morphologic, and molecular parallels with the serrated pathway (63). These features include a relatively high frequency of *BRAF* mutation, increased levels of methylation in the CpG island marker *MINT31* (64), a background of advanced serrated polyps, female preponderance, proximal predilection, and increased glandular serration within colorectal cancers. The families comprise affected individuals across several generations with 6 of 11 families fulfilling the Amsterdam I criteria. The families represent a novel syndrome of colorectal cancer originating through the serrated pathway of tumorigenesis. We have called this condition serrated pathway syndrome (SPS). Two examples of SPS families are shown in Fig. 2B.

Polyps and cancers from SPS families showed *BRAF* mutations at levels commensurate with that seen in individuals with HPP. *BRAF* mutations were found in 14 of 20 (70%) cancers and in 12 of 19 (63%) polyps in SPS families. In a series of HPP cases published recently, 45 of 68 (66%) polyps showed *BRAF* mutation (59). This compares with 15% seen in unselected colorectal cancers. In contrast, several studies have suggested that *BRAF* mutation is very rare in Lynch syndrome tumors, further delineating SPS as a separate entity (65, 66). Of 13 serrated polyps available for study in SPS families, five (39%) were ''advanced'' serrated polyps (SSA, SA, and MP). This level of advanced serrated lesions is ~10 times more frequent than that seen in a cohort of individuals attending an outpatient gastroenterology clinic. In that particular study, 65 of 1,436 (4.5%) polyps removed by colonoscopy were advanced serrated lesions (67). Interestingly, 2 of 42 subjects (4.8%) in the 11 SPS families met the criteria for the rare condition of HPP, suggesting that gene dosage may play a role in the serrated neoplasia phenotype. A summary of conditions with features of serrated neoplasia is given in Table 2.

The Nature of a Genetic Predisposition

Clues to the nature of the genetic change underlying these disorders can be gleaned from examination of molecular and pathology phenotypes. *BRAF* mutation is a frequent although not universal finding in SPS and HPP, and is always present as a somatic mutation. Although the underlying genetic causation of SPS families and HPP individuals is currently unknown, a reasonable explanation would implicate a genetic predisposition to (either directly or indirectly) hypermethylate multiple gene promoters. Evidence that a genetic mechanism could

Table 2. Features of colorectal cancer predispositions involving *BRAF* mutation and hypermethylation

Features	HPP	SPS	Sporadic CIMP CRC
MSI status of CRC	Predominantly MSS with occasional MSI-L and MSI-H (44, 45, 91)	Predominantly MSS with occasional MSI-L and MSI-H CRC (63)	At least 50% are MSI-H and the remainder are MSI-L or MSS (93)
Precursor lesions	Multiple serrated polyps and a lesser number of adenomas (51)	Sparse serrated polyps and adenomas present. Occasional individual has HPP	SSA (12). May present with synchronous serrated polyps and adenomas
Sex ratio and age of onset	Equal sex ratios, 54 y	Female preponderance, 58 y	Female preponderance, 74 y
Family history	Occasional first-degree relative with colorectal cancer (51), rare sibships, suggestive of codominant or recessive inheritance	Multicase colorectal cancer family, Amsterdam-like configuration	No family history
BRAF mutation	Up to 66% of lesions (59)	Up to 70% of lesions	In virtually all MSI-H CRC and up to 75% of the remainder
Methylation	CIMP is common (58, 59)	Methylation of *MINT31* 80%. Methylation of *MLH1* in all MSI-H cases	Widespread CIMP

Abbreviation: CRC, colorectal cancer.

underlie concordant hypermethylation and therefore serrated neoplasia has emerged from studies that have considered family history of cancer in association with CIMP. In a study from Frazier et al. (64), patients with CIMP cancers were 14 times more likely to have a family history of cancer than patients with cancers that did not show extensive DNA methylation. Further, concordant methylation and *BRAF* mutations are observed in the multiple lesions from individuals with HPP. Finally, reports from Samowitz and colleagues found a significant relationship between *BRAF* mutation and family history of colonic neoplasia in a large unselected study of over 800 individuals. Given the synergy between *BRAF* mutation and CIMP (7), this constitutes further evidence that a predisposition to hypermethylated gene promoters may be present in the population and could underlie novel syndromes of familial colorectal cancer (68, 69). Although there has been a single report to the contrary (70), the clinical rather than molecular ascertainment of Lynch syndrome families in this study is likely to have screened out SPS families as a consequence.

In imputing an epigenetic control defect, rather than an epimutation that targets only one promoter in the germ line (71), it might be assumed that CpG islands would undergo stochastic methylation events and would all be equally liable to do so. However, in CIMP colorectal cancer, some CpG islands are less likely to undergo hypermethylation than others. *MLH1* is frequently methylated in CIMP colorectal cancer, whereas both *MSH2* and *PMS2* are rarely methylated, despite the fact that these genes play essential roles in mismatch repair, have equally well-defined promoter CpG islands, and are involved in germ line mutations associated with Lynch syndrome. Conversely, CIMP affects the promoters of a wide variety of genes with no definitive role in colon tumor development, suggesting that not all *de novo* events are subject to growth selection (72). Further, evidence has been presented that particular sequence motifs are significantly overrepresented among promoters vulnerable to CIMP, implicating an underlying directive mechanism (72-74). Hence, control defects due to alterations in epigenetic regulators will target a subset of vulnerable loci, rather than all loci equally (7, 72, 75).

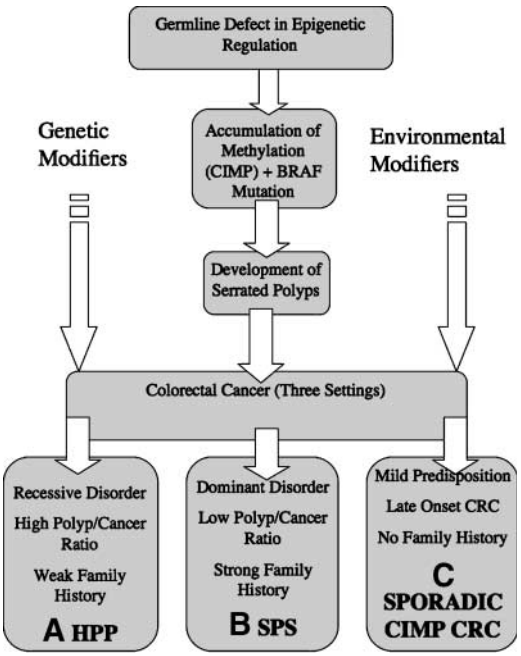

Figure 3. Three settings exemplify serrated neoplasia. **A.** HPP where numerous serrated polyps develop, and in which synchronous cancers may be present. **B.** SPS, which is a multicase and multigeneration colorectal cancer predisposition associated with advanced serrated polyps. **C.** Sporadic CIMP cancers where no evidence of family history is apparent but synchronous and metachronous lesions may be present. These three settings share molecular pathology phenotypes that suggest development from an epigenetic regulatory defect inherited as a recessive condition, an autosomal dominant disorder and a polymorphic variant, respectively.

Age-related hypermethylation has been observed in normal colonic mucosa (76) and has been postulated as a potential marker for field cancerization or a field defect (77), an area of abnormal tissue that has the potential to develop into a cancer (78). The area may appear essentially normal or may contain multiple discrete neoplastic lesions. It has previously been suggested that aberrant DNA methylation of tumor-suppressor genes may occur secondary to a genetic predisposition or to a field cancerization effect in the colon and may be useful as a molecular marker of colorectal cancer risk (79). Because sporadic MSI-H colorectal cancers are more likely to be multiple (80, 81) and of a serrated phenotype, it is also likely that subjects predisposed to MSI-H sporadic colorectal cancer have a field defect involving widespread hypermethylation. Consistent with this proposal, DNA hypermethylation has been reported more frequently from the normal colonic mucosa of patients bearing CIMP and sporadic MSI-H colorectal cancer (82, 83).

Genetic and Environmental Modifiers

Many cancers result from the combined effects of an inherited susceptibility and environmental influences. Although there is evidence for a genetic predisposition to DNA methylation, it is likely that lifestyle factors and genetic modifiers will also play a role. The magnitude of the contribution of lifestyle factors such as physical activity, body mass index, or use of aspirin and/or nonsteroidal anti-inflammatory drugs in the etiology of sporadic MSI-H colorectal cancers is currently not precisely fixed. However, studies of cigarette smoking and colorectal cancer have produced positive associations. Using data from a population-based, case-control study of colon cancer with case subjects ages between 30 and 79 years of age, Slattery et al. (84) found that cases with MSI-H colorectal cancer were more likely to smoke ≥20 cigarettes per day than case subjects with microsatellite stable (MSS) cancers. The association between MSI-H colorectal cancer and cigarette smoking was strongest among case subjects who started to smoke at a young age, smoked for ≥35 years, and were either current smokers or had stopped <15 years before diagnosis. A statistically significant linear trend of increased risk of MSI-H colorectal cancer was observed with increasing amount smoked. The study suggested that the attributable risk of smoking in MSI-related colorectal cancer is 21%. This has been confirmed by the finding that MSI colorectal cancer are more likely to arise in current smokers (85), and that smoking is associated with an increased risk of developing serrated lesions in individuals with a particular genotype (86).

Advances in Gastrointestinal Pathology and Implications for Surveillance

The role of serrated (hyperplastic) polyps in colorectal cancer development has gained increasing recognition in recent years due to evidence that a subset of these lesions are the likely precursors of sporadic MSI-H colorectal cancer (25). In addition, there is a growing awareness of the importance of screening in individuals with multiple serrated polyps (22, 51, 87), especially if dysplasia is evident (25) due to their increased risk of developing colorectal cancer. These insights

have highlighted the need for defining the morphologic criteria that characterize serrated polyps with increased malignant potential, notably SSA, and detailed guidelines have been proposed by several authors (12, 21, 25, 88, 89). However, lack of prospective studies, underreporting, and confusing terminology will inevitably delay the widespread dissemination and acceptance of these insights within the arena of clinical practice. Colorectal cancer mortality has been decreasing slowly in Western countries during the last decade, and the probable explanation for this is increased surveillance. Colorectal cancer has a particular feature that makes it amenable to prevention in that it is preceded by a premalignant polyp that can be removed safely. The inclusion of SSA among the polyps requiring surveillance and removal should contribute to the prevention of colorectal cancers with CIMP (90). Importantly, the discovery of the germ line alteration underlying SPS and HPP will identify the individuals and their families who are most at risk for the development of serrated neoplasia.

Conclusion and Hypothesis

Based on the co-occurrence of *BRAF* mutation, CIMP, and serrated neoplasia, and the segregation of these features in families with recessive and dominant modes of inheritance, we propose a model that implicates a genetic predisposition to (directly or indirectly) hypermethylate gene promoters as the fundamental defect underlying SPS and HPP (Fig. 3). We hypothesize that a germ line sequence alteration in a gene or genes, which results in an epigenetic regulatory defect, leads to the accumulation of somatic methylation events in tumor-suppressor genes, analogous to both the allele loss events in chromosomal instability colorectal cancer, and the frameshift deletions seen in MSI. Methylation events occurring in vulnerable tumor-suppressor genes will synergize with somatic oncogenic activation of *BRAF* and result in the development of serrated premalignant lesions. Given their increased tendency to multiplicity, we further suggest that ''sporadic'' MSI-H colorectal cancer may itself be the result of a comparatively mild predisposition of the type seen in HPP and SPS. The effect of smoking on the propensity to develop MSI-H colorectal cancer suggests a gene-environment interaction.

The transformation from serrated polyp to cancer is a relatively rare event and may constitute an important rate-limiting step involving the epigenetic inactivation of a critical tumor-suppressor gene. The serrated pathway displays considerable plasticity in its cancer end points, and resulting tumors may be MSI-H, MSI-L, or MSS (63, 91). Pathway commitment to these divergent end points is likely to be governed by factors such as germ line polymorphic variants and environmental insults. In summary, three phenotypic groups encompass a continuum of hypermethylation-associated colorectal cancer syndromes, including late-onset MSI-H ''sporadic'' colorectal cancer, individuals with HPP, and families with SPS.

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